REMARKS

Status of the Claims

Claims 1-6 are pending. Claims 4-6 are withdrawn from consideration as drawn to non-elected invention. Claims 1-3 are rejected. Claim 1 is amended. Claim 7 is newly added which is dependent on claim 1.

No new matter has been added. Reconsideration of the pending claims is respectfully requested.

The 35 U.S.C. §112 First Paragraph Rejection

Claims 1-3 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. This rejection is respectfully traversed.

Claim 7 has been added to define that the cell of claim 1 is of the HepG2-ΔRaf-1:ER cell line. As the Examiner pointed out, the specification is enabling for methods of inducing low density lipoprotein (LDL) receptor expression through contacting HepG2-ΔRaf-1:ER cells with ICI182,780, a compound that activates

p42/44^{MAPK}. As showed in Figure 2 and Example 10, HepG2-ΔRaf-1:ER cells have LDL receptors and p42/44^{MAPK} simultaneously, which can be exploited for such method. Therefore, Applicants respectfully submit that the specification fully enables a person having ordinary skill in this art to make and use the invention recited by claims 1-3 and 7. Accordingly, Applicants respectfully request that the rejection of claims 1-3 under 35 U.S.C. §112, first paragraph as being non-enabled be withdrawn.

The 35 U.S.C. §102 Rejection

Claims 1-3 were rejected under 35 U.S.C. §102(b) as being anticipated by **Kumar et al** (*J. Lipid Res.* 38: 2240-2248, 1997) or **Dhawan et al** (*FASEB J.* 13(4): part 1, pp. A194, March 1999). This rejection is respectfully traversed.

The Examiner states that **Kumar** teaches that TPA treatment of HepG2 cells leads to a 20-fold increase of mRNA levels of LDL receptor. In addition, **Kumar** inherently teaches a method

of inducing LDL receptor expression, independently of cell growth regulation, by activating p42/44^{MAPK}, thus anticipating claims 1-3.

Applicant respectfully argues that as amended, the claims are not anticipated by **Kumar** because **Kumar** does not teach, either expressly or inherently, that p42/44^{MAPK} activation induces cell growth arrest. In addition, **Kumar** teaches that p42/44^{MAPK} is activated subsequent to activation of protein kinase C-α (see Abstract), and not that the sole activation of p42/44^{MAPK} is sufficient to induce LDL receptor expression. Accordingly, Applicant respectfully requests that the rejection to claims 1-3 under 102(b) be withdrawn.

Furthermore, even though **Dhawan** teaches that activation of p42/44^{MAPK} is sufficient to induce LDL receptor expression in HepG2 cells, **Dhawan** does not teach that activation of p42/44^{MAPK} is not only independent of cell growth regulation, but also induces cell growth arrest as claimed herein. Accordingly, Applicant respectfully submits that the amended claim is not

Claims 1-3 were rejected under 35 U.S.C. §102(a) as being anticipated by **Dhawan** (*J. Lipid Res.* 40: 1911-1919, 1999). This rejection is respectfully traversed.

The Examiner states that **Dhawan** teaches the induction of LDL receptor in HepG2 cells by treatment with anisomycin, and that although a rapid and strong activation of $p46/54^{JNK}$ and $p38^{MAPK}$, but only a delayed and mild activation of $p42/44^{MAPK}$ occurred, the LDL expression induction depends solely on $p42/44^{MAPK}$. **Dhawan** also teaches that full activation of $p42/44^{MAPK}$ is required for full induction of LDL receptor expression, which implies that the extent of induction is dependent on the extent of $p42/44^{MAPK}$ activation.

Applicant respectfully submits that as amended, the present claims are novel over **Dhawan.** Although **Dhawan** teaches that activation of $p42/44^{MAPK}$ alone is sufficient to fully induce LDL receptor transcription independently of other cell growth signals (see Abstract and page 1917), **Dhawan** does not teach that activation of $p42/44^{MAPK}$ is independent of cell growth regulation

and induces cell growth arrest. The "cell growth signals" disclosed in the present description are in reference to previous research showing that induction of LDL receptor expression is induced by mitogens, growth factors and cytokines that induce cell growth, in a critical link to new membrane biosynthesis; see the paragraph spanning pages 29-30. **Dhawan** does not explicitly teach that p42/44^{MAPK} activation is able to induce LDL receptor expression independently of such cell growth signals. In addition, the present claims as amended disclose that p42/44^{MAPK} activation not only causes growth signal-independent LDL receptor expression, but that it concomitantly causes a decrease in cell proliferation and upregulation of genes associated with growth arrest (see the first full paragraph on page 30 and Example 14 of the present description). The present description suggests that growth arrest mediated by the p42/44^{MAPK} cascade may be a mechanism to prevent uncontrolled cell proliferation, as an alternative to apoptosis (page 32, lines 2-5).

Accordingly, Applicant respectfully submits that the amended claim is not anticipated by **Dhawan,** and requests that the rejection to claims 1-3 under 102(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed May 09, 2003. Applicants submit that the pending claims are now in condition for allowance. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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